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Review

The Role of Tumor Necrosis Factor and Interleukin 1 in the Immunoinflammatory Response

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Monocytes and tissue macrophages produce at least two groups of protein mediators of inflammation, interleukin 1 (IL-1) and tumor necrosis factor (TNF). Recent studies have emphasized that TNF and IL-1 modulate the inflammatory function of endothelial cells, leukocytes, and fibroblasts. Although these cytokines share a number of biologic properties, they have quite distinct gene and protein structures. It is our purpose to focus on the role of these mediators in inflammation.

KEY WORDS: inflammation; tumor necrosis factor; interleukin 1.

INTRODUCTION

Over the past 10 years information has accrued to suggest that protein cytokines, released by inflammatory cells, are important mediators of normal growth and differentiation. Mononuclear phagocytes have also emerged as cells central to the drama played out at sites of inflammation. Although these cells release a plethora of inflammatory mediators, two of the more important cytokines, interleukin 1 (IL-1) and tumor necrosis factor (TNF), appear to play an important role in the orchestration of many of the immune processes. Both IL-1 and TNF have a profound effect on tissue remodeling, repair, and inflammation by coordinating the activities of many other cells, including endothelial cells, granulocytes, osteoclasts, fibroblasts, hematopoietic cells, and lymphoid cells. An important concept to emerge from these studies is the idea that under physiological conditions cytokines play a role in the homeostasis of cells and tissue. Processes of inflammation and response to injury are associated with augmented release of these protein mediators and frankly toxic or life-threatening syndromes, e.g., cachexia, shock, etc., result from their exaggerated prolonged release.

TNF and interleukin 1 designate two distinct groups of proteins. These cytokines have many related and overlapping biological functions which are described below. The biochemical basis for the redundant functions of these proteins is not well understood. However, many of the highly purified recombinant interleukins are being shown to be pleotropic in their actions. Direct comparisons of the linear amino acid compositions of TNF and IL-1 reveal no homology between the proteins and only short sequences of homology between members of each group of proteins. In addition, there is no overlap in receptor binding. Recent computer simulations of the secondary structures predict that both proteins will contain eight β strands and no α helices. Circular dichromism studies are consistent with these predictions: the proteins may be composed of two four stranded β sheets packed together in the form of a β-sandwich like elastase and other serine proteases (1).

In this review we emphasize the roles of these cytokines in the initiation and maintenance of the inflammatory process. Recent reviews have emphasized the antitumor and cachexia-inducing properties of TNF (2–5).

INTERLEUKIN 1

Gene Structure and Proteins

There are at least two major forms of IL-1 that possess different isoelectric points (6). The pI 5.0 form has been called IL-1α, whereas the pI 7.0 form is termed IL-1β. Human (7,8) and mouse cDNAs (9) have been cloned for each of these proteins, and among the human proteins there is 26% amino acid identity (10). Figure 1 presents a comparison of the primary amino acid sequences of these proteins. Both IL-1α and IL-1β are first synthesized as intracellular precursor proteins of approximately 270 amino acids which yield extracellular molecules of approximately 17 kd. In addition to the soluble 17-kd forms of IL-1, a 23-kd membrane-associated form has been found on several cells including macrophages (11) monocytes (12), dendritic cells (13), and fibroblasts (14). IL-1 activity was originally shown to be produced by macrophages and monocytes. More recently, IL-1 message has been found in most nucleated cells. The murine interleukin 1 genes are located on chromosome 2 near β2-microglobin, an interesting association given the location of the TNF genes near the major histocompatibility complex (MHC) genes (15). There may be other members of the IL-1 gene family becuase the IL-1 activities derived from Epstein–Barr B-cell lines (16) and U937 histiocytic lymphoma cells (17) appear to have unique biochemical properties (18). In addition, lower molecular weight fragments (10,

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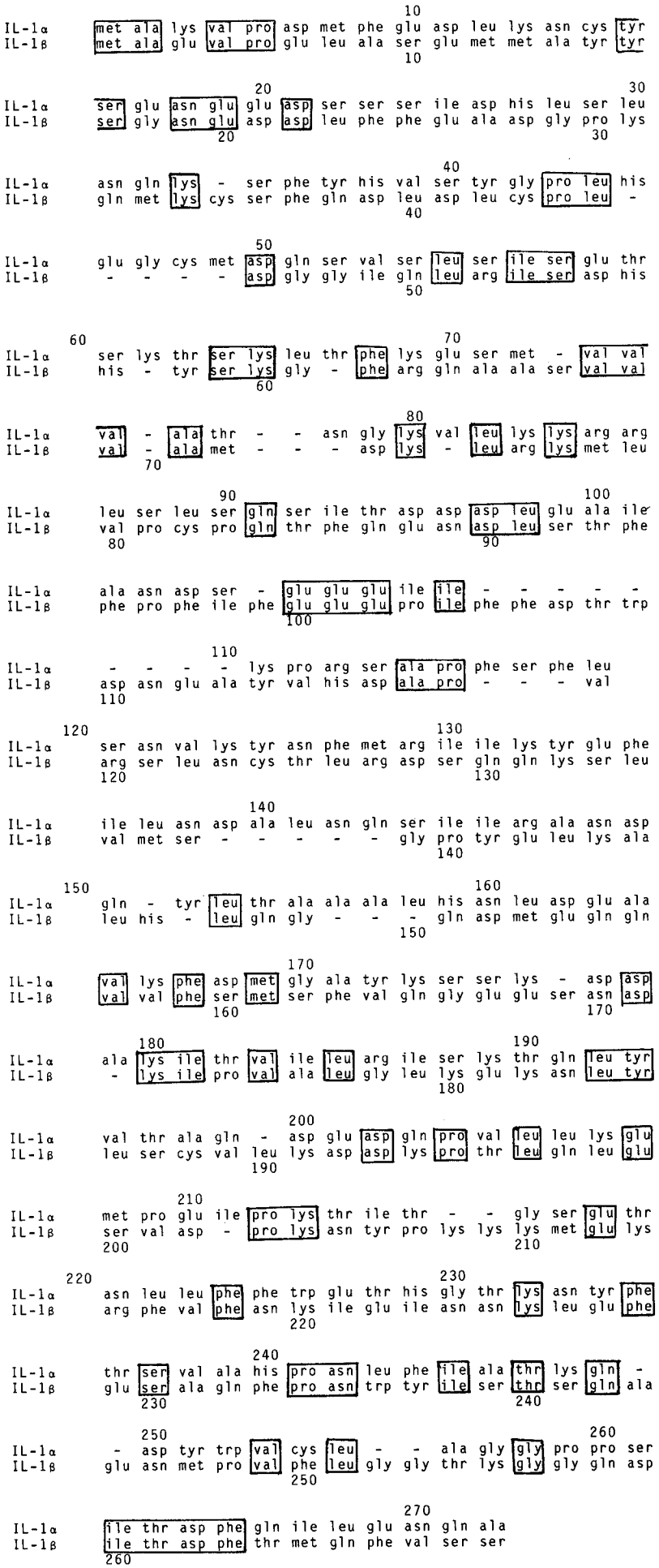

Fig. 1. Comparison of the linear amino acid structures of IL-1α and IL-1β. The shared amino acids are enclosed in the boxes.

4, and 2 kd) of IL-1 possess some of the biologic properties of the 17-kd secreted form (18,19). The findings that recombinant IL-1β autocatalytically degrades into these bioactive fragments is consistent with the structural studies suggesting homology between IL-1 and proteases (1,20). Recently a nonapeptide corresponding to residues 163–171 was shown to have the adjuvant but not the inflammatory properties of recombinant IL-1 (21).

Receptors

A wide variety of cell types binds and responds to IL-1 (22–24). Dower and co-workers (22) showed that mouse and human fibroblasts had 2000 to 5000 receptors/cell for ^{125}I-labeled human IL-1β. Competition studies showed that human IL-1α and IL-1β bind to the same receptor on a human Epstein–Barr virus (EBV)-transformed B-cell line (25) and on murine EL-4 thymoma cells (26). EL-4 cells express 1000 to 1500 receptors/cells, while EBV-transformed B cells express only 100–200 receptors/cell, with an affinity of 2.0 to 6.0 $\times$ 10^{-10} M for human IL-1β. IL-1 receptors are required for responsiveness of a cell or tissue. IL-1-responsive murine thymocytes (PNA^+; peanut agglutinable) bound IL-1, whereas, IL-1-unresponsive PNA^- thymocytes did not bind IL-1 (24). The IL-1 responsive LBRM-33-1A5 murine lymphoma cell line has about 500 receptors/cells (22,23).

Cross-linking studies suggest that one subunit of the IL-1 receptor has a M_r in the 60- to 80-kd range (22,25). More recent work suggests that a 41-kd protein with tyrosine kinase autophosphorylation activity may associate with this 60- to 80-kd subunit to form the IL-1 receptor (27). There is no evidence that the TNFs or the interferons bind to the IL-1 receptor.

TUMOR NECROSIS FACTOR

Gene Structure and Proteins

TNF was first described in 1975 by Carswell *et al.* (28), as a serum-derived factor from bacillus calmette guerin (BCG)-primed endotoxin-treated mice or rabbits that produced hemorrhagic necrosis of certain tumors *in vivo* and was cytotoxic or cytostatic to certain tumor cell lines *in vitro*. A related factor, initially called lymphotoxin (LT), with similar biological properties, is synthesized by mitogen-stimulated lymphocytes (29,30). Because TNF and LT have structural and functional homology, they have been called TNFα and TNFβ, respectively.

Cloning of the human TNFα cDNA showed that the mRNA encodes a precursor protein of 233 amino acids (31–33). The mature molecule is a nonglycosylated protein of 17.3 kd containing a single disulfide bridge. Recent evidence suggests that TNFα may exist in dimeric or trimeric forms (34). TNFα lacks a typical N-terminal signal sequence and the 76 N-terminal residues may act to anchor the protein into the cell membrane (M. Kreigler, personal communication). Cloning of the TNFβ cDNA showed that the mRNA encodes a protein of 205 amino acids (35). The first 34 of these constitute a conventional signal sequence. Unlike TNFα, TNFβ is a glycosylated protein with no cysteine residues. TNFα and TNFβ share about 30% amino acid identity, with two highly conserved regions (amino acids 35–66 and 110–133 in TNFα) that may be important for receptor binding. Figure 2 presents a comparison of the primary amino acid sequences of these proteins. The genes for both human TNFα and TNFβ are separated by about 1 kb of DNA on chromosome 6 within the major histocompatibility complex (36,37).

Receptors

Specific, saturable, high-affinity TNFα receptors have been found on many cell types (38–44). TNFα and TNFβ appear to share the same or a very similar receptor (38). Various workers (3,4,42) showed that a series of human tumor cell lines with markedly different sensitivities to TNF cytotoxicity expressed 5000–10,000 receptors/cell, with a K_d of 2 $\times$ 10^{-10} M. Other workers have also shown that TNF receptors are necessary, but not sufficient for cells to be affected by TNF. Granulocytes have 1500–2000 receptors/cells, with a K_d of 2 $\times$ 10^{-10} M (43). Interestingly, interferon γ enhances the specific binding of TNF to cells (38,45,46), apparently by increasing the TNF receptor number. The small (2- to 3-fold) increase in TNF receptor number induced by interferon γ probably does not account for the marked (10- to 1000-fold) synergism exhibited by TNF and IFN γ on virus-infected cells (47).

Cross-linking studies have given disparate values for the M_r of the TNF receptor. Murine cells have two polypeptides of 75 and 95 kd that can be cross-linked to TNF (41); the human TNF receptor has a M_r of 60–80 kd (44) by similar techniques. Creasey *et al.* (40) found several polypeptides (54, 75, 95, and 138 kd) involved in binding TNF (40). One of these (138 kd) was not detected in a TNF-resistant breast cancer cell line.

THE IMMUNOINFLAMMATORY RESPONSE

Inflammation and Cell-to-Cell Communication

Increasing scientific evidence supports the role of macrophage-derived monokines as essential signal transmitters during an inflammatory reaction (49,50). The production and regulation of these signals are crucial to the normal cell-to-cell communication that occurs during the initiation, maintenance, and resolution of specific foci of inflammation. When this communication becomes altered by either the exaggerated or the diminished production of these signals, pathologic consequences usually result. Disease states resulting from a hyperimmune response can be as devastating as those resulting from a hypoimmune response.

Table I presents a heuristic concept unifying some of what is known about the actions of cytokines such as TNF and IL-1. Under normal conditions these substances act as local mediators of cellular homeostasis. The precise function of the membrane versus soluble forms of these mediators is unclear. However, because the mononuclear phagocytes penetrate many tissues, they may deliver these signals directly to cells they contact. When a tissue is injured, the augmented release of monokines helps orchestrate its repair. The exaggerated or prolonged release of a peak of material may lead to cachexia, multiorgan failure, or death as originally postulated by Beutler and Cerami (2). TNF and IL-1 play an important role during the various phases of disease

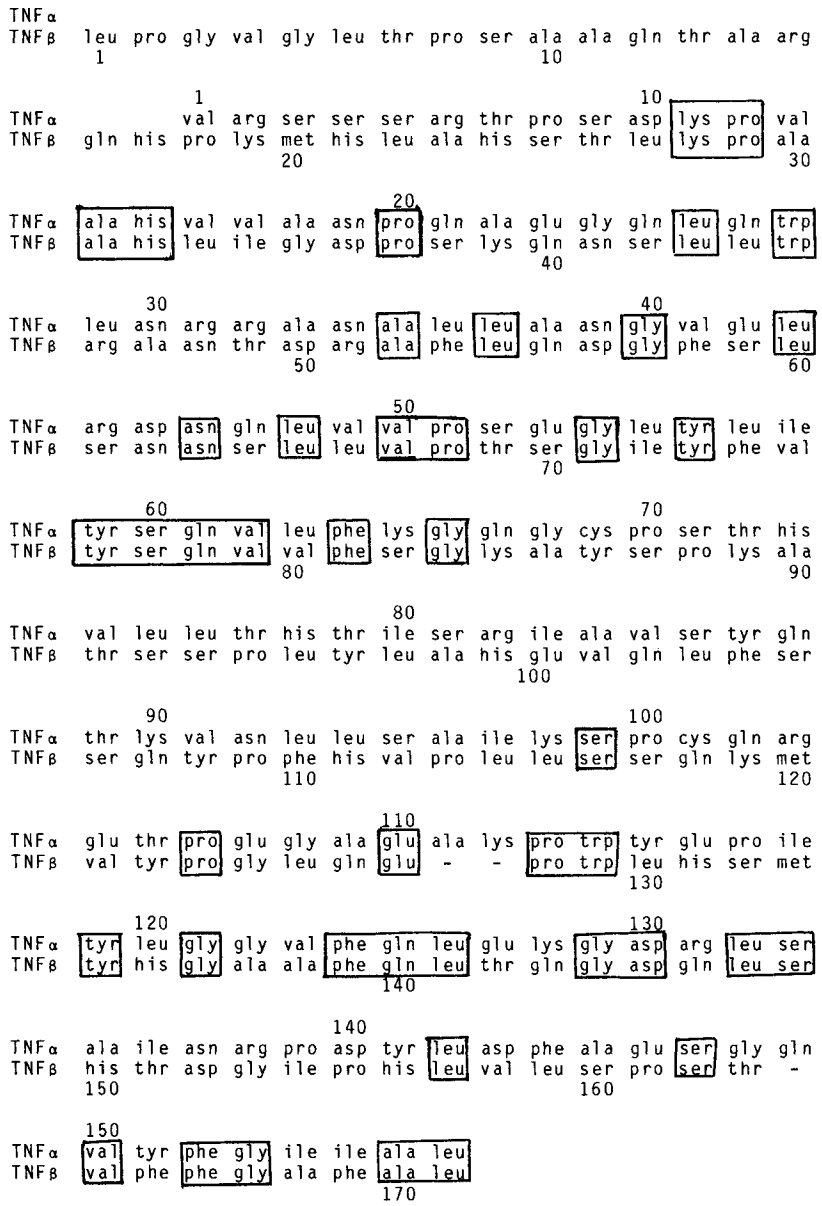

Fig. 2. Comparison of the linear amino acid structures of TNFα and TNFβ. The shared amino acids are enclosed in the boxes.

states, since they have a direct impact on a variety of cellular targets (see Fig. 3). Thus, they influence both immunologic and physiologic systems. The capacity of TNF and IL-1 to mediate inflammatory and physiologic responsiveness via their roles as signal transmitters in cell-to-cell communication is described below.

Vascular Endothelial Cells

Vascular endothelial cells (ECs) play a key role in various inflammatory processes and must now be included as active participants during an immune response. TNF and IL-1 have been demonstrated to communicate directly with

Table I. Monokines and Cell Tissue Homeostasis

Monokine concentration	Low	Medium	High
Site of action	Cells	Tissue	Systemic
Monokine form	Membrane low secreted	Membrane secreted	Secreted
Function	Trophic growth factor, coordinate homeostasis, circadian control?	Inflammation, tissue repair acute phase, fever	Cachexia, acute phase, septic shock, hypotension, multiple organ, intravascular coagulation

ECs and regulate many of the activities associated with surface molecule expression. Both cytokines induce a procoagulant state. For example, IL-1 induces the synthesis of plasminogen activator inhibitor (51) and both molecules induce a tissue factor-like procoagulant activity (52,53). Normally, ECs express thrombomodulin which binds to serum proteins S and C (54) to promote local anticoagulation. ECs are converted from a participant in an anticoagulation state to a procoagulation state (54), because the EC expression of thrombomodulin and the hepatic snythesis of protein C is suppressed by TNF and IL-1 (see Fig. 4). This procoagulation state is induced during endotoxemia when high levels of these monokines are released. Interestingly, activated protein C (55) can block many of the metabolic and hematologic effects of endotoxin, presumably by reversing the local procoagulant state initiated by TNF, by IL-1, and directly by LPS (54,56).

In addition to the EC procoagulant state induced by TNF and IL-1 (56), the ECs become "sticky" for circulating inflammatory cells including neutrophils, lymphocytes, and monocytes (58). Adherence of these cells to ECs is a critical step in the formation of an inflammatory infiltrate at a site of tissue injury. The molecules that mediate the adhesion are members of the LFA group of the surface proteins denoted by the CD11/CD18 markers (59). TNF and IL-1 cause a rapid expression of these molecules by both ECs and circulating white cells (52,55). In addition, they stimulate the rapid expression of the intercellular adhesion molecule 1 (ICAM-1) and other surface antigens associated with EC activation (e.g., H4/128) (57,60).

The effects of TNF on the vascular endothelium are not restricted to adherence proteins and the coagulation pathway, because TNF has been shown to stimulate endothelial cells to produce granulocyte/monocyte colony-stimulating factor (61), interleukin-1 (62), and class I major histocompatibility molecules (63). The pleomorphic effects that TNF exerts on the endothelium are further evidence that this monokine is an important mediator of immune and physiologic processes.

Granulocyte Activation

Granulocytes, particularly neutrophils, are important participants in the acute inflammatory process. TNF and IL-1 promote the accumulation of granulocytes at sites of inflammation by enhancing the expression of CD11/CD18 surface adherence molecules on granulocytes and endothelial cells (59). TNFα appears to be a much more potent stimulus for neutrophil adherence to endothelial cells than TNFβ (62). In addition, TNFα enhances the respiratory burst (43,64–67), degranulation (66), phagocytosis, and antibody-dependent cellular cytotoxicity (ADDC) of neutrophils (67). TNFβ also enhances neutrophil-mediated antibody-dependent cellular cytotoxicity of chicken red cells (67). TNFα markedly augments the capacity of eosinophils to mediate ADCC for schistosomes (68).

Some workers claim that IL-1 promotes release of both specific and azurophilic granules from neutrophils (69,70) and stimulates reduction of nitroblue tetrazolium (NBT) dye, a measure of the oxidative burst (71). Conflicting results exist regarding whether TNF and IL-1 are directly chemotactic for granulocytes (72–74). Despite this controversy,

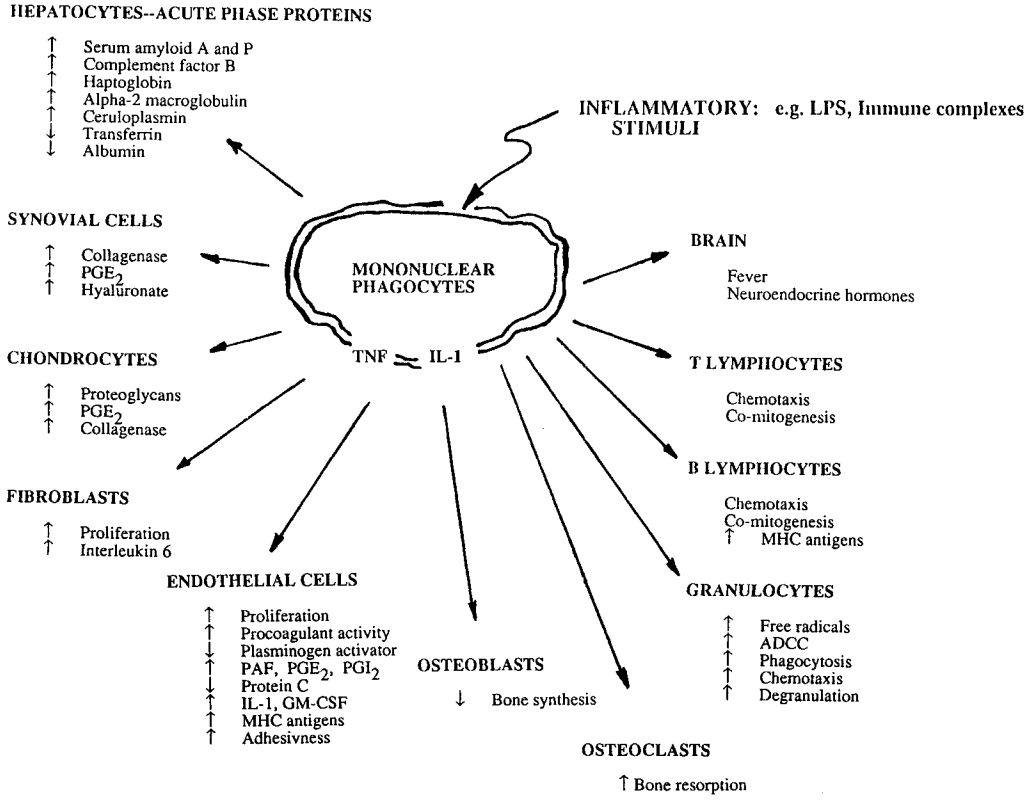

Fig. 3. The pleiotropic actions of IL-1 and TNF.

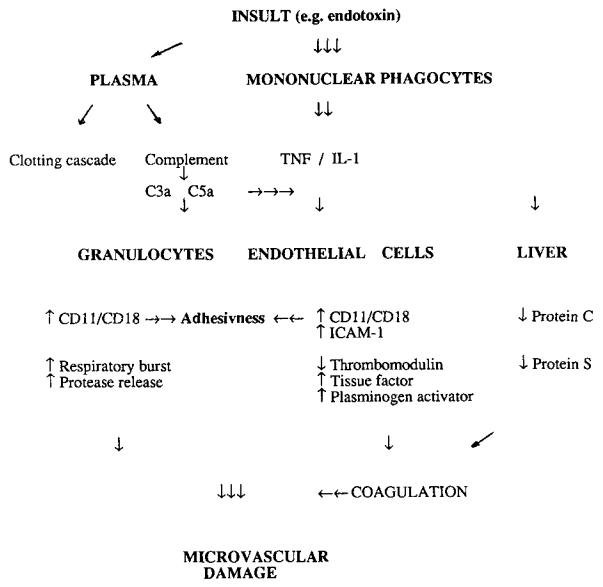

Fig. 4. Pathogenesis of TNF- and IL-1-mediated microvascular injury.

low concentrations of IL-1 given intradermally cause accumulation of granulocytes and can initiate or provoke the local Shwartzman reaction (75), a model of tissue inflammation characterized by microthrombi, neutrophil infiltration, and hemorrhagic necrosis in the skin. In addition, intravenous injection of IL-1 or TNF produces a neutrophilia by mobilizing mature neutrophils from the bone marrow (76,77).

Connective Tissue

Remodeling of connective tissue is a normal physiologic process mediated by macrophages, fibroblasts, and the enzymes and extracellular substances they produce. Both TNF and IL-1 induce the release of collagenase and arachidonate metabolites by cultured synovial cells and fibroblasts (78–81). IL-1 induces at least three metalloproteinases that degrade gelatin, collagen, and proteoglycan. Interleukin 1 activity is spontaneously released from mononuclear cells isolated from synovial tissue obtained from patients with rheumatoid arthritis (82) and may contribute to the pathology of the affected joint by increasing the formation of the pannus.

Over 15 years ago, Horton *et al.* (83), described a lymphokine obtained from stimulated peripheral white cells that promoted bone resorption. When this osteoclast-activating factor was purified, it was found to be identical to IL-1β (84). It is now known that TNFα and TNFβ have a similar osteoclast-activating activity (84). Additional evidence by Bertolini *et al.* (85) showed that bone collagen synthesis was inhibited by these cytokines and that the content of alkaline phosphatase, a marker of osteoblast function, was decreased. Several clinical studies suggest that the hypercalcemia and bone destruction associated with multiple myeloma, adult T-cell lymphoma, and Burkitt's lymphoma may be associated with the release of these cytokines by the cancerous cells (86,87) or the inflammatory state associated with them.

In addition to bone resorption, cartilage resorption occurs in many rheumatological diseases including osteoarthritis and rheumatoid arthritis (88). IL-1 promotes the degradation of proteoglycan and inhibits its de novo synthesis (89,90). Although less potent, TNF also stimulates resorption of proteoglycan in explanted cartilage (89) and this effect is additive with IL-1 (91).

Proliferation of fibroblasts accompanies normal tissue repair at foci of inflammation. Under normal conditions, IL-1 and TNF are growth factors for fibroblasts (92,93), and the exuberant release of these cytokines at sites of inflammation may contribute to joint destruction, granulomatous lesions, and fibrosis after chronic inflammatory stimuli. Although TNF appears to have intrinsic mitogenic activity for fibroblasts, Le *et al.* (94), have shown that TNF can also induce the synthesis of both IL-1α and IL-1β in human fibroblasts. The potent mitogenic effect of TNF has been demonstrated at a concentration of 10^{-10} *M*, which is similar to the K_d for its binding to the TNF receptor. Interestingly, the mitogenic effect of TNF is synergistic with the growth-promoting activities of insulin and epidermal growth factor (EGF) (95). TNF and IL-1 undoubtedly have a role in normal bone and cartilage repair and remodeling: in inflammation exaggeration of these process may contribute to tissue damage.

GENERAL METABOLIC EFFECTS OF TNF AND IL-1

Fever. Elevation of body temperature is one of the most primitive responses to infection. It was postulated several decades ago that phagocytes released a protein that produced fever (96). Subsequently, workers showed that fever was mediated by prostaglandins generated in the anterior hypothalamus. Furthermore, it was shown that aspirin and other inhibitors of the cyclooxygenase pathway of arachidonate metabolism had their antipyretic effects directly in the brain by blocking prostaglandin E_2 (PGE_2) synthesis (97). Recently, both IL-1α and IL-1β were shown to cause fever (19), and purified endogenous pyrogen shares many, if not all, of the properties attributed to IL-1 (96).

Recombinant TNF (1 μg/kg) also produces a monophasic fever similar to IL-1 (98). At higher doses (10 μg/kg), TNF produces a biphasic fever, the second peak resulting from the release of IL-1 by TNF. Rimsky *et al.* (16) have reported a novel IL-1 derived from a B-cell line which has many of the activities of IL-1 except that it is not pyrogenic. The effect of elevated temperature on different aspects of inflammation is not well understood, although it is known that various immunological reactions including thymocyte comitogenesis (99,100) are increased at elevated temperatures. In addition, TNF shows augmented cytotoxicity for mouse L cells and tumor cells (101–102) at temperatures of 39–40°C. The physiologic effects of these monokines may be extremely diverse, since IL-1 (and possibly TNF) has been postulated to be an important regulator of diurnal circadian rhythms (M. Kluger, personal communication).

Sleep. IL-1β and TNF have been shown to enhance slow-wave sleep in rabbits (103). Higher levels of IL-1 have been detected in cerebrospinal fluid (CSF) of cats (104) during sleep compared to waking. Sleep deprivation augments IL-1 activity in human plasma (105). These findings may account at least in part for the disturbances of sleep associated with infectious and inflammatory states.

Stress Hormones–Neuroendocrine–Central Nervous System (CNS) Effects. Recombinant IL-1β can directly stimulate pituitary cells to release adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), growth hormone (GH), and thyroid-stimulating hormone (TSH) *in vitro* (107) and corticotropin-releasing factor (CRF) *in vivo* (108,109). These studies provide evidence for a feedback circuit between the immunoinflammatory system and the neuroendocrine system. This circuit is undoubtedly very important in the orchestration of an individual's response to the stresses of infectious and inflammatory states.

The Acute-Phase Response. Infection and inflammation are accompanied by various metabolic derangements of the liver. These include the increased synthesis of so-called acute-phase proteins such as C-reactive protein, serum amyloid A protein, ceruloplasmin, and various complement proteins (110). There is a concomitant decrease in synthesis of transferrin with a decrease in serum iron and zinc. These metabolic changes in hepatocytes are mediated by IL-1 (111). Although not as fully investigated, TNF also appears to stimulate the acute-phase response (112).

Cachectin Activity. Beutler, Cerami, and co-workers (2,113–116) have characterized a protein produced by macrophages that suppresses the synthesis of lipoprotein lipase in the murine preadipocyte cell line 3T3-L1. They postulated that this protein, called cachectin, caused the hypertriglyceridemia and wasting associated with chronic infections and cancer. Subsequent studies showed that the N-terminal sequence of purified cachectin is identical to TNF (114). In adipocytes, lipoprotein lipase is suppressed by TNF/cachectin, at the level of transcription. Torti *et al.* (117) showed that TNF also suppresses the transcription of several other adipocyte differentiation-specific genes. In keeping with biologic activities, IL-1 also blocks the synthesis of lipoprotein lipase by 3T3-L1 cells (113,118). Thus, both of these proteins, as well as interferon γ (119) (which causes hypertriglyceridemia in treated patients), produce a catabolic state that could theoretically provide critical nutrients to cells fighting infection. In sepsis, chronic infections, or uncontrolled cancer hyperstimulation of the mononuclear phagocyte system to overproduce monokines has been postulated to lead to multiple organ failure, wasting, and death of the host (2). A prime example of this catabolic state is Gram-negative sepsis and shock, a serious disease state initiated by endotoxin that undoubtedly involves exaggerated macrophage activation and TNF production (2,115).

Immunoregulation. Interleukin 1 was originally described as a lymphocyte-activating factor (LAF) (120) and its comitogenic activity is the basis of IL-1 bioassays (121). IL-1 acts early in the activation of T cells. It induces the expression of IL-2 receptors on T cells activated by phytohemagglutinin (PHA) or anti-CD3 antibodies (122,123) and promotes the secretion of IL-2 (124,125). IL-1 is also known to be a growth and differentiation factor for B lymphocytes (126–128). Thus, IL-1 is one of the primary factors released by accessory cells to communicate with both humoral and cellular arms of the immune response.

The role of TNF in immunoregulation is not well studied. T lymphocytes can be stimulated by high concentrations of TNFα to release interferon γ (129) and synthesize IL-2 receptors (130). TNF potentiates the mitogenesis of B cells (131) and T cells *in vitro* (120). TNF must act after the initial stimulation of T cells because resting T cells appear to lack TNF receptors. (41).

Hematopoiesis. Maintenance and amplification of the inflammatory response require the sustained production of inflammatory cells by the bone marrow. IL-1 is a potent colony-stimulating factor for bone marrow cells (133), whereas TNF appears to inhibit growth of hematopoietic cells *in vitro* (134). IL-1 stimulates fibroblasts to release granulocyte–macrophage colony-stimulating factor (GM-CSF) (135). Interleukin 1 (136,137) and TNFα (61,136) both stimulate endothelial cells to produce G-CSF and GM-CSF. Interestingly, TNFβ fails to stimulate GM-CSF production by endothelial cells (138).

REGULATION OF TNF AND IL-1

Many stimuli cause cells to release TNF and IL-1. Binding of immune complexes and phagocytosis by mononuclear phagocytes augments their release of TNF and IL-1. In addition, interferon γ, CSF-1, endotoxin, phorbol esters, various viruses, and poly(I:C) all induce increased transcription of the IL-1 and TNFα genes (3,4,139,140). Complement fragments C3a (141) and C5a (142) augment release of IL-1, and substance P, a neurotransmitter released at sites of so-called neurogenic inflammation (143), was recently shown to induce secretion of both TNF and IL-1 from macrophages (144).

Several second-messenger pathways appear to be operative in mononuclear phagocytes. For example, initiation of the inflammatory response is accompanied by marked changes in the metabolism of arachidonate acid by mononuclear phagocytic cells. Of particular interest is the coincidental production of prostaglandin E_2, along with various monokines, suggesting that this arachidonate metabolite may serve as an endogenous regulatory molecule. Recent studies have demonstrated that LPS stimulation of Ia-positive macrophages results in the production of TNF, IL-1, and PGE_2 (145,146). A rapid rise in release of the proteins is followed by an accelerated, linear increase in PGE_2. A plateau in IL-1 and TNF occurs when elevated levels of PGE_2 are found in the macrophage supernatant. Further studies using exogenously added PGE_2 have demonstrated a suppressive effect on the release of macrophage-derived IL-1 and TNF (147). Although PGE_2 blocks TNF and IL-1 production by macrophages, PGE_2 has no effect on the toxic effects induced by preformed TNF. While PGE_2 suppresses macrophage-derived IL-1 and TNF production, the inhibition of the cyclooxygenase pathway by indomethacin augments transcription and release of macrophage-derived IL-1 and TNF (127,128). Both TNF and IL-1 augment prostacyclin synthesis by cultured vascular endothelial cells (148) and the synthesis of thromboxane B_2 from granulocytes and macrophages (149). The *in vivo* toxicity of preformed TNF can be blocked by inhibitors of the cyclooxygenase pathway (150). PGE_2 receptors activate adenyl cyclase and generate a cyclic AMP second messenger, and agents that elevate cyclic AMP levels (e.g., cAMP, 8-bromo cAMP, dibutryl cAMP, pentoxyfylline) inhibit transcription of TNF (151). Glucocorticoids (e.g., dexamethasone, prednisone, hydrocortisone, cortisone) but not mineralocorticoids suppress the transcription of TNF and IL-1, possibly by inducing li-

pocortin, which blocks phospholipase A (4,140,152). Inhibition of protein kinase C by H7 [1-(5 - isoquinolinylsulfonyl)-2-methylpiperazine] blocks the release of both TNF and IL-1 from macrophages, whereas the calmodulin inhibitor W7 [*N*-(6-aminohexyl-5-chloro-1-naphthalenesulfonamine] blocks the release of only IL-1 (153). Thus both metabolites of arachidonate and phosphoinositol participate in the regulation of IL-1 and TNF transcripton. Calmodulin-regulated kinases may also regulate IL-1 transcription.

How TNF and IL-1 mediate their effects on target cells has been the subject of much work and speculation. Receptor binding undoubtedly initiates various second-messenger cascades, the details of which are still unclear. The IL-1 receptor may have tyrosine kinase activity and transduce ligand binding signals via phosphorylation (27). Inhibition of phospholipase A by quinacrine or Rosenthal's inhibitor is known to inhibit TNF-mediated mouse L-cell cytotoxity (154). Indomethacin (at high concentrations known to be a phospholipase A inhibitor) and lipoxygenase pathway inhibitors NDGA and diethylcarbazine also block the cytotoxicity of TNF (154). Very interesting are the findings linking TNF susceptibility/cytotoxicity with the generation of oxygen free radicals (106). TNF may mediate some of its actions by modulating cellular glutathione levels which buffer the cell from free radical stresses. Studies with recombinant tumor growth factor β suggest that this cytokine antagonizes many of the activities of TNF (129,155). The mechanism of this antagonism is unclear.

TNF and IL-1 both induce the synthesis of interleukin 6 [interferon β2, β cell stimulating factor (BSF-Z)] (156–158) and metalothionine (159). TNF induces IL-1 transcription (52,98,140) and the transcription of classes I and II MHC molecules (63), 2′,5′-oligo(A) synthetase, and the acute-phase proteins noted above (4,110). TNF is known to inhibit the transcription of several proteins, including c-*ras,* c-*myc,* tumor growth factor β (TGFβ), lipoprotein lipase, the transferrin receptor, and the CD4 molecule (3,4,160). *In vivo* TNF suppresses the cytochrome P450 system (161). What role these up- or down-regulated proteins play in TNF- and IL-1-mediated or normal cell growth control, inflammation, cytotoxicity, or viral killing will require further investigation. A particularly interesting phenomenon is the marked synergism observed between some cytokines. For example, TNF and interferon γ have pronounced synergistic antiproliferative and antiviral effects (3,4,47). While it is beyond the scope of this review to describe the extensive literature on antiproliferative and antiinfectious properties of TNF and IL-1, it should be noted that this synergism makes beautiful biological sense. Interferon γ released by T cells stimulates mononuclear phagocytes that release TNF and IL-1 to provoke a double attack on virus-infected cells.

THERAPEUTIC INTERVENTION

Therapeutic intervention in inflammatory states caused by exuberant release of protein cytokines can theoretically take place at several levels. These are as follows: (a) block the substance or agent initiating the inflammatory cascade, e.g., antibodies or antibiotics to block bacteria or their toxic products such as endotoxin (162); (b) block release of the cytokines; (c) neutralize the cytokines or their receptors; and (d) prevent the inflammatory response from amplifying itself by blocking the participating cells or their products (e.g., coagulation proteins).

As noted above, pretreatment of rats given TNF with inhibitors of cyclooxygenase blocks the toxic effects of TNF (146). This suggests that metabolites of the arachidonate pathway may mediate some of the deleterious effects of this cytokine. The finding that inhibitors of thromboxane synthetase can block the lethal effects of lipopolysaccharide (LPS) (163) suggests that the procoagulant state induced in microvascular cells contributes to the pathogenesis of LPS-mediated inflammation. Other drugs that modify this procoagulant state would be expected to have a similar effect. In this regard, Taylor and co-workers (55) have shown that activated protein C reversed some of the vascular effects of endotoxemia in baboons. Anti-CD18 monoclonal antibodies that block the molecules involved in cell adherence have been shown to block cellular traffic into areas of inflammation (164). Monoclonal antibodies that neutralize activation of the complement cascade (165) or the clotting cascade may also prevent cell activation during the early phase of inflammation.

It seems likely that directly inhibiting TNF and IL-1 with monoclonal antibodies (166) or receptor antagonists will modulate inflammatory reactions. For example, Cerami and co-workers (167) have shown that an anti-TNF monoclonal $F(ab')_2$ administered to baboons prior to a lethal *Escherichia coli* bacteremic infection can prevent septic shock and death. Efforts are under way in several laboratories to generate nontoxic antagonist muteins of these proteins (168). It is also possible that agents could be identified that bind the cytokines, changing them from agonists to antagonists. Regulation of monokine activity by natural inhibitors has been suggested by a number of studies. Several putative IL-1 inhibitors have been identified from urine (169–171), EBV-transformed B cells (172), neutrophils (173), and myelomonocytic cells (174), as well as other sources (175,176). Uromodulin, derived from the urine of pregnant women, has been cloned and shown to be identical to the Tamm-Horsfall glycoprotein (171).

Substances that block the release of TNF and IL-1 should be useful therapeutics. Steroids act on endothelial cells and are known to block the transcription of the TNF and IL-1 genes (4) and may reduce inflammation and the toxicity of sepsis at least partially by this mechanism. Prostaglandin E_2 has a similar effect (140). Whether more specific inhibitors (e.g., antisense oligonucleotides to block transcription of these factors) can be developed will require more work.

SUMMARY

A complex array of mediators is produced by mononuclear phagocytes at sites of inflammation. Among the most intensely studied in recent years are the proteins, TNF and IL-1. These biochemically distinct cytokines coordinate many of the activites of the cells involved in generating an inflammatory response. Endothelial cells, myeloid cells, fibroblasts, osteoclasts, lymphoid cells, hepatocytes, and hematopoietic cells are known to be affected. It is possible that novel therapeutic strategies can be developed to block the action of these proteins.

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